(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 February 2005 (17.02.2005)

PCT

(10) International Publication Number
WO 2005/014479 A2

(51) International Patent Classification[7]: C01B 35/10, A61K 51/02, 49/00

(21) International Application Number: PCT/EP2004/008830

(22) International Filing Date: 5 August 2004 (05.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0318728.3	8 August 2003 (08.08.2003)	GB
0416141.0	19 July 2004 (19.07.2004)	GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS

(57) Abstract: A novel process for preparing radiolabelled compounds by incorporation of radioactive carbonyl groups into precursors, which are then used to make the radiolabelled compounds. These radiolabelled compounds have a number of uses including in vivo imaging techniques such as positron emission tomography.

WO 2005/014479 A2

Process

Field of The Invention

The present invention relates to a process for preparing radiolabelled compounds. More specifically, the present invention relates to a process for preparing radiolabelled compounds, which involves incorporation of radioactive carbonyl groups into precursors, which are then used to make the radiolabelled compounds. These radiolabelled compounds have a number of uses including in vivo imaging techniques such as positron emission tomography.

Background of the Invention

Positron emission tomography (PET) is a non-invasive imaging technique that offers high spatial and temporal resolution and allows quantification of tracer concentrations in tissues. The technique involves the use of radiotracers labelled with positron emitting radionuclides, which permit measurement of parameters regarding the physiology or biochemistry of a variety of living tissues.

Compounds can be labelled with positron or gamma emitting radionuclides. The most commonly used positron emitting (PET) radionuclides are ^{11}C, ^{18}F, ^{15}O and ^{13}N, which are accelerator produced, and have half lives of 20.4, 109.8, 2 and 10 minutes respectively. Due to their short half-lives ^{11}C, ^{15}O and ^{13}N labelled radiopharmaceuticals have to be use at the site of production and require the development of specific synthetic procedures.

^{11}C ($T_{1/2}$=20.4min) is an important neutron-deficient radionuclide for PET because it can substitute for non-radioactive carbon in any organic molecule without altering their biological and physiochemical properties. An important part of the elaboration of new procedures to incorporate PET radionuclides into molecules is the development and handling of new ^{11}C labelled precursors.

^{11}C can be produced in the absence of the naturally occurring stable isotopes ^{12}C and ^{13}C, and with high yields on a small proton accelerator using the $^{14}N(p,\alpha)^{11}C$ reaction in a target gas containing nitrogen (Christman, et al., 1975; Clark, et al., 1975 and Welch et al., 1968). In the presence of oxygen trace (e.g. 0.1% oxygen), the radiochemical species formed is [^{11}C]carbon dioxide which is suitable for use directly as in the ^{11}C-carboxylation of Grignard

reagents (organomagnesium halides). [^{11}C]carbon dioxide can also be converted into a variety of secondary radiolabelled chemical entities such as high specific activity [^{11}C]methyl iodide.

An important consideration for radiolabelling with carbon-11 is the maximization of specific activity of the radiolabelled compound. Isotopic dilution of [^{11}C]carbon dioxide with atmospheric carbon dioxide (3.4×10^4 ppm) substantially reduces its specific activity and therefore limits the application of the resultant radiolabelled compound as a PET probe.

As an alternative method to using [^{11}C]carbon dioxide for radiolabelling compounds, [^{11}C]carbon monoxide may be used instead, as it is less prone to isotopic dilution with atmospheric carbon monoxide (0.1 ppm). Methods for the production of [^{11}C]carbon monoxide by reducing [^{11}C]carbon dioxide using reducing metals at high temperatures are well known (Gmelins 1972; Clark, et al., 1975; Zeisler, et al.,1997). Zinc and molybdenum are the most widely used reducing agent for the [^{11}C]carbon dioxide/carbon monoxide conversion.

However, it is difficult to trap ^{11}CO in the small volume of organic solvent in which most of the precursors for the production of radiolabelled compounds are soluble. Small volumes of solvent are required because this allows easy isolation of the radiolabelled product by means of preparative HPLC and increases the concentration of the starting materials in the reaction mixture, thereby forcing the reaction in the desired direction.

In 1978 Roeda, et al., described a method for the production of [^{11}C]phosgene from [^{11}C]carbon monoxide however, its practical use in the production of radiopharmaceuticals has been very limited due low yields and the lack of suitable equipment and methods to efficiently trap and react carbon monoxide.

Existing methods for the trapping of [^{11}C]carbon monoxide for the production of radiolabelled compounds rely on the use of high pressure or recirculation of [^{11}C]carbon monoxide to maintain adequately high levels of [^{11}C]carbon monoxide in solution (Kihlberg, et al., 1999; Hostetler, et al., 2002). This requires the use of dedicated automated robotic systems for the handling of [^{11}C]carbon monoxide and specialised equipment.

Borane carbonyl (H_3BCO) is the immediate precursor to boranocarbonates, such as the potassium salt $K_2[H_3BCO_2]$ which were reported to release CO in water at elevated

temperatures in 1967 (Malone et al., 1967; Malone et al., 1967a). Although yields of the solid, air stable $K_2[H_3BCO_2]$, produced from the known methods of B_2H_6 + CO are good, it is not convenient to work under pressurised conditions with $H_3B.CO$, as it is a pyrophoric gas (Carter, et al., 1965; Mayer, 1971). Alberto et al., (**2001**) found that by preparing $H_3B.CO$ from commercially available $H_3B.THF$ and reacting it in situ with an alcoholic solution of potassium hydroxide, $K_2[H_3BCO_2]$ could be produced at ambient pressures. This result was achieved by controlling the equilibrium of the two-way reaction between H_3BCO and $H_3B.THF$ by selectively condensing the THF out of the reaction. The resultant $K_2[H_3BCO_2]$ was then used as an in situ source of CO in aqueous solution and as a reducing agent.

It has now been found that radiolabelled $H_3B.CO$ can be used to release radiolabelled carbon monoxide in organic solvents, aqueous solvents and mixtures of organic and aqueous solvents in order to prepare radiolabelled compounds without the need for high pressure autoclaves or recirculation units.

Brief Summary of the Invention

Accordingly, in a first aspect the invention provides a process for the preparation of radiolabelled $H_3B.CO$ comprising contacting H_3B in a suitable solvent with carbon monoxide and a suitable base, characterised in that the carbon monoxide is radiolabelled.

Radiolabelled $H_3B.CO$ may be prepared by the reaction of borane (H_3B) in a suitable solvent with radiolabelled carbon monoxide. Suitable solvents for this reaction are those which solubilize H_3B and allow it to co-ordinate with free electron pairs of the oxygen, for example tetrahydrofuran (THF) and ethers such as diethyl ether and dioxane. THF is preferred as a solvent due to its physical characteristics of a high boiling point, a lower affinity towards water and its comparable low price.

Hydrides of other elements, such as aluminium gallium, indium and thallium hydride would also be expected to co-ordinate with radiolabelled carbon monoxide. However, the instability of aluminium hydride in solvents suitable for this reaction means that if an aluminium compound were to be used it would preferably be compounds such as $AlCl_3$ in THF or aluminium tri organyls.

Free solvent may be removed from the reaction by condensation or other suitable means such as a solid support. This achieves the advantage of shifting the equilibrium of the reaction towards increased production of radiolabelled $H_3B.CO$.

The carbon monoxide used in the reaction may be labelled by any conventional method with any of the following isotopes ^{11}C, ^{13}C, ^{14}C, ^{15}O or ^{18}O. Preferably ^{11}C is used.

Suitable solvents for use in the process of the invention include ethers such as diethyl ether and dioxane, and tetrahydrofuran. Preferably tetrahydrofuran is used. Suitable mixtures of solvents may also be used.

In a second aspect the invention provides the use of radiolabelled $H_3B.CO$ prepared according to the first aspect of the invention, as a donor of radiolabelled carbon monoxide in the manufacture by carbonylation of radiolabelled compounds.

In practice the second aspect of the invention may be carried out by using the radiolabelled $H_3B.CO$ prepared according to the first aspect of the invention in a coupling reaction as set out in Scheme 1 below, in which coupling reactions are typically carried out with a halide or a triflate (trifluoromethanesulfonate) with a nucleophile (alcohol, amine, thiol) or a organostannane, a base and a catalyst such as a palladium(0) catalyst to obtain esters, amides, ketones, aldehydes, carboxylic thioesters or by reacting a nitro component or an azido derivative to form isocyanate derivatives or condensing two nucleophiles in presence of selenium to synthesized carbamates, thiocarbamates, carbonates and ureas.

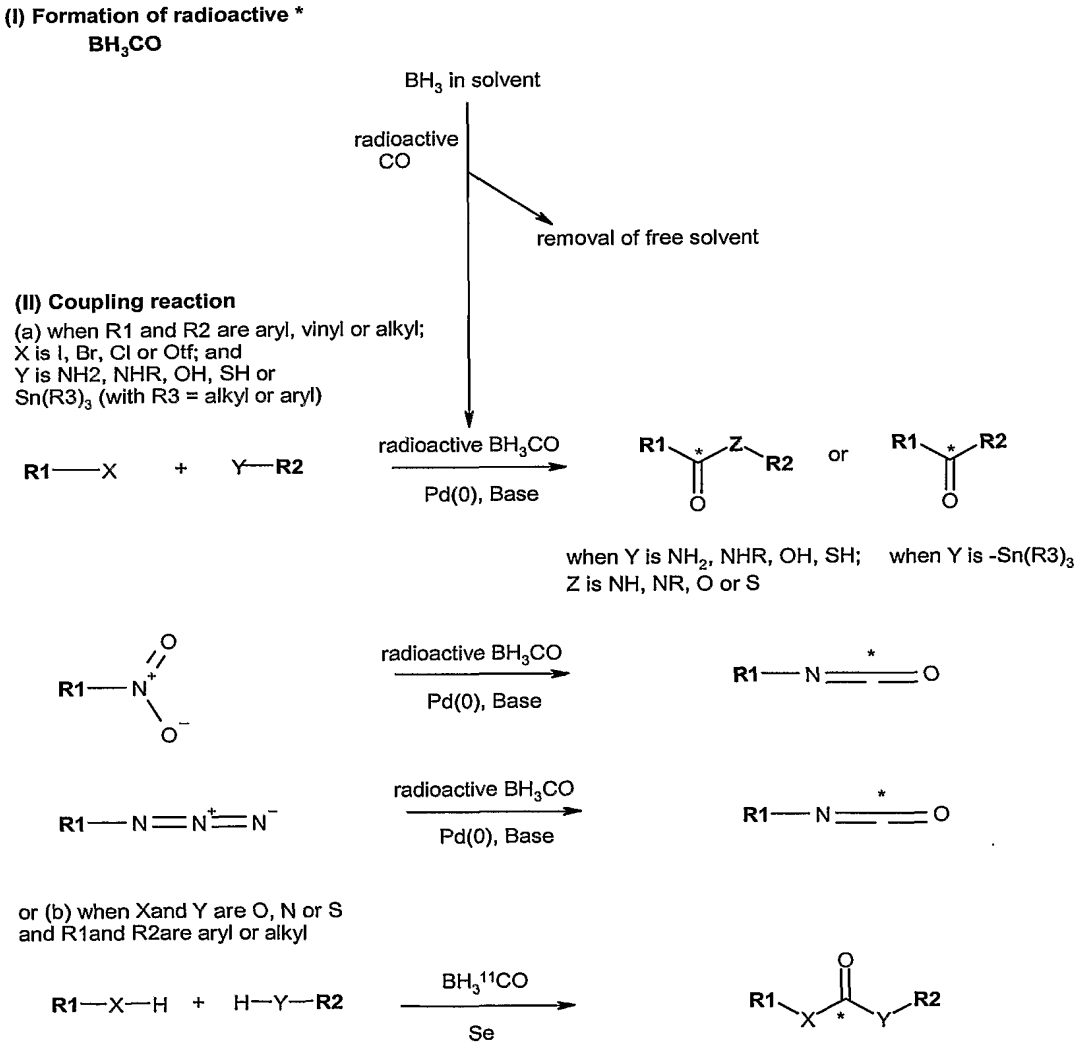
Suitable bases for use in the process of the invention include triethylamine (TEA), N-Methyldibutylamine (MDBA), M-Methyl-2,2,6,6-tetramethylpiperidine (N-MTMP) and *N,N*-di-isopropyl-ethylamine (DIPEA). Suitable mixtures of bases may also be used.

The starting materials and reagents for use in the first and second aspects of the invention are available commercially or can be synthesised by well-known and conventional methods. The reaction conditions used in the formation of non-radiolabelled $H_3B.CO$ can be sourced from Alberto et al., (2001), other reaction conditions such as the radiolabelling of CO and carbonylation reactions are well known.

$[^{11}C]CO$, prepared by reduction of $[^{11}C]CO_2$ with a reducing metal (commonly zinc or molybdenum), is trapped using conventional methods such as molecular sieves in liquid

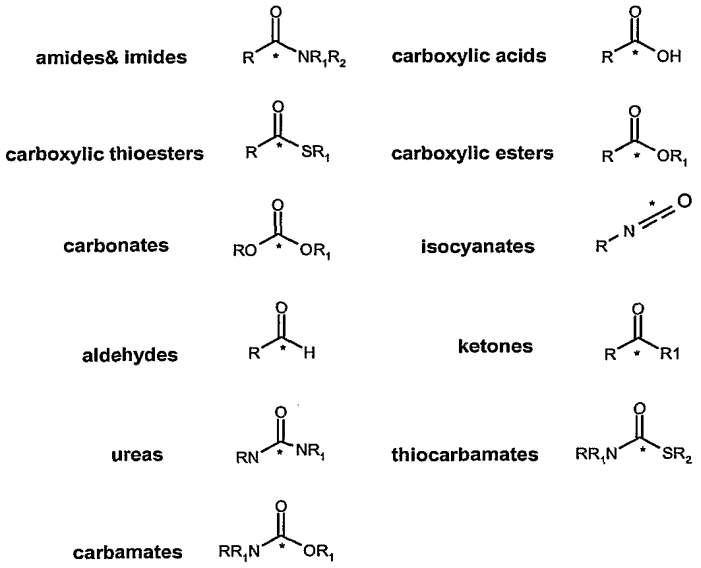
nitrogen or silica and is then carried into a solution of BH_3•THF using an inert gas carrier. The [^{11}C]borane carbonyl ([^{11}C] $H_3B.CO$) complex thus formed is then carried through to a reaction chamber in which it is reacted with suitable components to construct the required compound using conventional coupling methods. Conventional coupling reaction often take place at elevated temperatures and the reaction chamber may be made of materials suitable for use in a microwave (such as glass).

In order to promote the formation of the [^{11}C]borane carbonyl THF is removed from the reaction, typically by condensation. Coupling reactions are typically carried out reacting [^{11}C]borane carbonyl with the appropriate starting materials and reagents as depicted in scheme 1.



Scheme1

Suitable compounds for radiolabelling by this method are those which contain a carbonyl group (some examples are shown in Scheme 2).



Scheme 2

Amides and imides can also contain lactams and carboxylic esters can also contain lactones.

In a third aspect the invention provides radiolabelled $H_3B.CO$ prepared in accordance with the first aspect of the invention.

In fourth aspect the invention provides radiolabelled compounds prepared by carbonylation in accordance with the second aspect of the invention.

Edidepride (*N*-((S)-1-Ethyl-pyrrolidin-2-ylmethyl)-3-iodo-5-methoxy-benzamide) , FLB (5-bromo-*N*-((S)-1-ethyl-pyrrolidin-2-ylmethyl)-2,3-dimethoxy-benzamide) and raclopride (3,5-dichloro-*N*-((S)-1-ethyl-pyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxy-benzamide), which are all dopamine D2 ligands and PK11195 (1-(2-Chloro-phenyl)-isoquinoline-3-carboxylic acid), which is a benzodiazepine receptor ligand are commonly used PET ligands that contain carbonyl groups that can be labelled with [^{11}C]CO.
In a fifth aspect the invention provides use of the radiolabelled compounds according to the fourth aspect of the invention in imaging techniques such as positron emission tomography,

modified single photon emission tomography and autoradiography (classical and phosphor imaging plates).

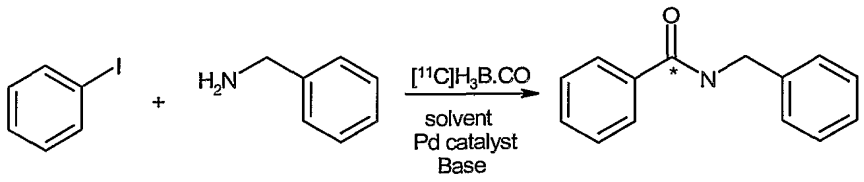
In a sixth aspect the invention provides a composition comprising a radiolabelled compound in accordance with the fourth aspect of the invention and a pharmaceutically acceptable carrier or carriers, suitable for use in the above mentioned imaging techniques.

Detailed Description of the Invention
The invention is further described through the following examples:

Examples

Abbreviation list:
THF: Tetrahydrofuran
TEA: Triethylamine
DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene
TMP: Tetramethylpiperidine
DMF: Dimethylformamide
DIPEA: *N,N*-di-isopropyl-ethylamine
MDBA: *N*-Methyldibutylamine
N-MTMP: M-Methyl-2,2,6,6-tetramethylpiperidine

Synthesis of [^{11}C]*N*-benzyl-benzamide (I)



Example 1

Preparation of the reaction vial

Palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 700 μL THF (degassed by bubbling N_2 through it for few minutes). Then,

iodobenzene (1.5 mg, 0.00735 mmol) and benzylamine (1.2 mg, 0.011 mmol) dissolved in 300 μL THF (degassed by bubbling N_2 through it for few minutes) were added to the solution of palladium complex. TEA (1.6 μL, 0.0088 mmol) was added, and the reaction vial was placed in the reaction-setup in a bath at -78°C.

Synthesis

[^{11}C]Carbon dioxide was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using a nitrogen gas target (containing 1% oxygen) pressurised to 150 psi and bombarded with 16 MeV protons using the General Electric Medical Systems PETtrace 200 cyclotron. Typically, the irradiation time was 30 minutes using a 40 μA beam current. After irradiation, [^{11}C]carbon dioxide was trapped and concentrated on 4Å molecular sieves. The trapped [^{11}C]CO_2 was released from molecular sieves in a stream of nitrogen (30 mL/min) by heating them to 350°C. [^{11}C]CO_2 was reduced on-line to [^{11}C]carbon monoxide after passing through a quartz tube filled with zinc granular heated to 400°C. The produced [^{11}C]carbon monoxide was transferred in our system set-up at 30 mL/min, where it was condensed on 4Å molecular sieves at -196°C. After 6 min delivery and trapping of the [^{11}C]CO, the radioactive gas was then released at room temperature in a flow of nitrogen (6 mL/min) to bubble through a BH_3.THF solution (1.5 mL of a 1.0 M solution) in order to make the [^{11}C]BH_3.CO complex. This complex was carried with the flow of nitrogen through an empty vial cooled at -60°C to remove the THF, and finally through the reaction vial containing the reactants (cf. preparation of the reaction vial above) cooled at -78°C. The trapping process took approximately 6 min (when the radioactivity level measured in the reaction vial has reached a maximum). The delivery tubings were then removed and the reaction vial heated in an oven at 110°C for 10 min. The crude product was filtered through a 0.45 μm filter and analysed using analytical radio HPLC.

Analytical HPLC was performed using a Dionex system (SUMMIT HPLC system), equipped with a Dionex HPLC pump (Model P 680A LPG) with a 200 μl injection loop connected in series with a Phenomenex Sphereclone 5u ODS(2) column (250 x 4.60 mm, 5 μm), a variable Dionex UV/VIS detector (Type UVD 170U/340U) in series with a sodium iodide radiodetector of in-house design.

The desired end-product was identified by co-injection with a non-radioactive reference. The given yields of the product are based on the final radioactivity trapped in the reaction vial at EOS (End Of Synthesis).

The analytical HPLC showed the formation of the desired radiolabelled [^{11}C]*N*-benzylbenzamide in Example 1 in approximately 1.7% yield.

Example 2

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 1 except that the palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 700 μL of a solution of THF:H_2O, 4:1 (degassed by bubbling N_2 through it for few minutes), the iodobenzene (1.5 mg, 0.00735 mmol) and benzylamine (1.2 mg, 0.011 mmol) were dissolved in 300 μL of a solution of THF:H_2O, 4:1 (degassed by bubbling N_2 through it for few minutes). The reaction vial was placed in the reaction-setup in a bath at 0°C and after the trapping of the [^{11}C]BH_3.CO the reaction vial was heated at 120°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired radiolabelled [^{11}C]*N*-benzylbenzamide in approximately 7% yield.

Example 3

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 1 except that the palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 700 μL of a solution of THF + 2% H_2O (degassed by bubbling N_2 through it for few minutes), the iodobenzene (1.5 mg, 0.00735 mmol) and benzylamine (1.2 mg, 0.011 mmol) were dissolved in 300 μL of a solution of THF + 2% H_2O (degassed by bubbling N_2 through it for few minutes) and after the trapping of the [^{11}C]BH_3.CO, the reaction vial was heated at 120°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 30% yield.

Example 4

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 1 except that the palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 700 μL of a solution of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes), the iodobenzene (1.5 mg, 0.00735 mmol) and benzylamine (1.2 mg, 0.011 mmol) were dissolved in 300 μL of a solution of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes) and after the trapping of the [^{11}C]BH_3.CO the reaction vial was heated at 50°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 17% yield.

Example 5

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 4 except that after the trapping of the [^{11}C]BH_3.CO, the reaction vial was heated at 70°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 47% yield.

Example 6

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 4 except that after the trapping of the [^{11}C]BH_3.CO, the reaction vial was heated at 85°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 47% yield.

Example 7

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 4 except that after the trapping of the [^{11}C]BH_3.CO, the reaction vial was heated at 120°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 47% yield.

Example 8

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 4 except that after the trapping of the [^{11}C]BH_3.CO, the reaction vial was heated at 140°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide was approximately 28% yield.

Example 9

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 5 except that DBU (1.3 μL, 0.0016 mmol) was used instead of TEA. The analysis of the HPLC chromatograms showed traces of the formation of the desired [^{11}C]*N*-benzylbenzamide.

Example 10

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 5 except that 2,2,6,6-TMP (1.7 μL, 0.009 mmol) was used instead of TEA. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 8% yield.

Example 11

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 5 except that pyridine (0.7 μL, 0.0088 mmol) was used instead of triethylamine and the reaction vial was heated from 40 to 80°C for 15 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 28% yield.

Example 12

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 5 except that benzylamine (3.6 mg, 0.034 mmol) was used instead of TEA and the reaction vial was heated 90°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 20% yield.

Example 13

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 4 except that the palladium(II) diacetate, triphenylphosphine, iodobenzene and benzylamine benzylamine were dissolved in DMF, and after the addition of TEA the reaction vial was placed in the reaction-setup in a bath at -50°C. After the trapping of the [^{11}C]BH_3.CO the reaction vial was heated at 90°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 23% yield.

Example 14

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 4 except that the palladium(II) diacetate, triphenylphosphine, iodobenzene and benzylamine benzylamine were dissolved in 1,2-dichloroethane, and after the addition of TEA the reaction vial was placed in the reaction-setup in a bath at -20°C. After the trapping of the [^{11}C]BH_3.CO the reaction vial was heated at 110°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 12% yield.

Example 15

Preparation of the reaction vial

Preparation of the reaction vial was carried out as described in Example 1 except that the palladium (II) diacetate (0.5mg, 0.0022mmol) and triphenylphosphine (2.9 mg, 0.11mmol) were dissolved in 700 μL THF with 1% H_2O and the iodobenzene (1.5mg, 0.00735 mmol) and benzylamine (1.2 mg, 0.011 mmol) were dissolved in 300 μL degassed THF with 1% H_2O.

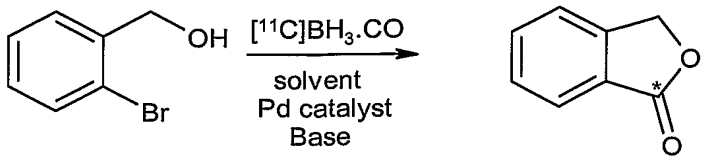
Synthesis

Synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 1 except that the produced [^{11}C]CO was condensed onto a trap at –196 °C made from a 12-inch coil of 1/16" stainless steel tubing, 0.040" i.d., packed with carbonex 1000, 45/60 mesh (Supelco). After 6 min delivery and trapping of the [^{11}C]CO, the radioactive gas was then released at room temperature and carried out through an empty vial in a flow of nitrogen (6 mL/min) into a reactor loaded with the BH_3•THF solution (1.5 mL of a 1.0 M solution in THF) in order to form the [^{11}C]BH_3.CO complex. The complex was then carried with the flow of nitrogen through an empty vial cooled at -78 °C, and finally through the reaction vial containing the reactants cooled at -78 °C. After 6 min of delivery of the [^{11}C]BH_3.CO complex the tubings were removed and the reaction vial heated in an oven at a temperature o 95°C for 10 min. The crude product was filtered through a 0.45 μm filter and analysed for radioactivity contentThe analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 47% yield.

Example 16

The synthesis of [^{11}C]*N*-benzyl-benzamide was carried out as described in Example 15 except that the TEA was replaced with DIPEA (1.53μL, 0.0088 mmol) and the reaction vial containing the [^{11}C]BH_3.CO complex was heated in an oven at 90°C for 10 min, filtered and analysed for radioactivity content The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]*N*-benzylbenzamide in approximately 91% yield

Synthesis of [^{11}C]phthalide



Example 17

Tetrakis(triphenylphosphine)palladium(0) (1.1 mg, 0.95μmol) was dissolved in 500 μL of a solution of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes). Then, a mixture of 2-bromobenzyl alcohol (1.1 mg, 0.006 mmol) and K_2CO_3 (5 mg, 0.036 mmol) were dissolved in 300 μL of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 1, the reaction was heated at 100°C for 4 min, filtered and analysed for radioactivity content The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]phthalide in traces.

Example 18

Palladium(II) diacetate (0.8 mg, 0.0035 mmol) and triphenylphosphine (5 mg, 0.020 mmol) were dissolved in 700 μL of a solution of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes). Then, a mixture of 2-bromobenzyl alcohol (2.2 mg, 0.012 mmol) and K_2CO_3 (5 mg, 0.036 mmol) were dissolved in 300 μL of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 1, the reaction was heated at 120°C for 5 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]phthalide in traces.

Example 19

Palladium(II) diacetate (0.8 mg, 0.0035 mmol) and triphenylphosphine (5 mg, 0.020 mmol) were dissolved in 700 μL of a solution of THF (degassed by bubbling N_2 through it for few minutes). Then, a mixture of 2-bromobenzyl alcohol (2.2 mg, 0.012 mmol) and DBU (2.0 μL, 0.014 mmol) was dissolved in 300 μL of THF (degassed by bubbling N_2 through it for few minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in

Example 1, the reaction was heated at 110°C for 5 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]phthalide in traces.

Example 20

Palladium(II) diacetate (0.8 mg, 0.0035 mmol) and triphenylphosphine (5 mg, 0.020 mmol) were dissolved in 700 μL of a solution of THF (degassed by bubbling N_2 through it for few minutes). Then, a solution of 2-bromobenzyl alcohol (2.2 mg, 0.012 mmol) in 300 μL of THF (degassed by bubbling N_2 through it for few minutes) was added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 1, the reaction was heated at 120°C for 5 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]phthalide in approximately 40% yield.

Example 21

Palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 700 μL of a solution of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes). Then, a mixture of 2-bromobenzyl alcohol (2.2 mg, 0.012 mmol) and TEA (1.9 μL, 0.014 mmol) were dissolved in 300 μL of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 1, the reaction was heated at 90°C for 8 min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]phthalide in approximately 26% yield.

Example 22

Palladium(II) diacetate (1.0 mg, 0.0044 mmol) and triphenylphosphine (6 mg, 0.022 mmol) were dissolved in 700 μL of a solution of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes). Then, a mixture of 2-bromobenzyl alcohol (2.2 mg, 0.012 mmol) and TEA (1.9 μL, 0.014 mmol) were dissolved in 300 μL of THF + 1% H_2O (degassed by bubbling N_2 through it for few minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 1, the reaction was heated at 90°C for 8 min, filtered and analysed

for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]phthalide in approximately 20% yield.

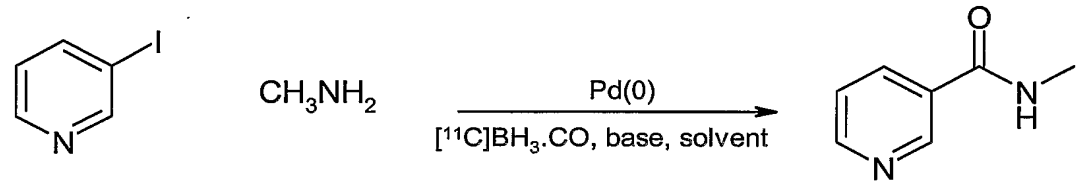
Example 23

Palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 700 μL of a solution of THF with 1% H_2O (degassed by bubbling N_2 through it for few minutes). Then, a mixture of 2-bromobenzyl alcohol (1.37mg, 0.0073 mmol) and DIPEA (1.53µL, 0.0088 mmol) were dissolved in 300 μL of THF with 1% H2O (degassed by bubbling N2 through it for few minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78C. The trapping of the [^{11}C]BH_3.CO complex was carried out as described in Example 15 and the reaction was heated at 95°C for 10min, filtered and analysed for radioactivity content. The analysis of HPLC chromatograms showed the formation of the desired [^{11}C]phthalide in approximately 40% yield.

Example 24

The synthesis of [^{11}C]phthalide was carried out as described in Example 23 except that the reaction was heated at 95°C for 8min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]phthalide in approximately 89% yield min

Synthesis of [^{11}C]*N*-Methylnicotinamide

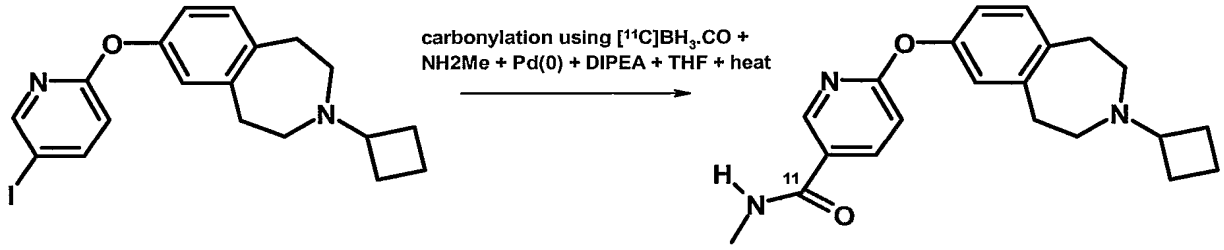


Example 25

Palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 400 μL of a solution of THF with 1% H_2O (degassed by bubbling N_2 through it for 5 minutes). Then, a mixture of 3-iodopyridine (1.5mg, 0.0073 mmol) and DIPEA (1.53µL, 0.0088 mmol) were dissolved in 600 μL of methylamine 2.0 M in solution in THF and then added to the solution of the palladium complex. The reaction vial was placed in the

reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 15, the reaction was heated at 140 °C for 8min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C] *N*-Methylnicotinamide in approximately 95% yield

Synthesis of [^{11}C]6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-*N*-methylnicotinamide (WO 2004/056369)



Example 26

Palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 700 μL of a solution of THF with 1% H_2O (degassed by bubbling N_2 through it for 5 minutes). Then, a mixture of 3-cyclobutyl-7-[(5-iodo-2-pyridinyl)oxy]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (3.1mg, 0.0073 mmol), DIPEA (1.53μL, 0.0088 mmol) and methylamine 2.0 M (0.011mmol, 5.48μL solution in THF) were dissolved in 300 μL of THF with 1% H2O (degassed by bubbling N2 through it for 5 minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 15, the reaction was heated at 100 °C for 8min ,filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-*N*-methylnicotinamide in approximately 6.5% yield.

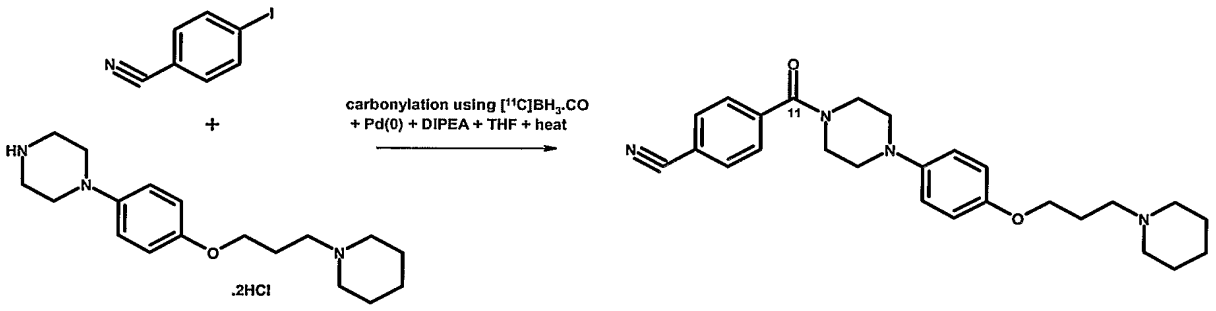
Example 27

Palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 400 μL of a solution of THF with 1% H_2O (degassed by bubbling N_2 through it for few minutes). Then, a mixture of 3-cyclobutyl-7-[(5-iodo-2-pyridinyl)oxy]-

2,3,4,5-tetrahydro-1*H*-3-benzazepine (1.6 mg, 0.00365 mmol), DIPEA (1.53μL, 0.0088 mmol) and methylamine 2.0 M (0.011mmol, 5.48μL solution in THF) were dissolved in 300 μL of THF with 1% H2O (degassed by bubbling N2 through it for 5 minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 15, the reaction was heated at 140 °C for 8min , filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [^{11}C]6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-*N*-methylnicotinamide in approximately 44.4% yield

Example 28

Synthesis of [^{11}C](4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanoyl)-benzonitrile (WO 2004/035556)



Palladium(II) diacetate (0.5 mg, 0.0022 mmol) and triphenylphosphine (2.9 mg, 0.011 mmol) were dissolved in 700 μL of a solution of THF with 1% H_2O (degassed by bubbling N_2 through it for 5 minutes). Then, a mixture of 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (2.05mg, 0.0055 mmol), DIPEA (1.86μL, 0.011 mmol) and 4-iodo-benzonitrile (0.0036mmol, 0.85mg) were dissolved in 300 μL of THF with 1% H2O (degassed by bubbling N2 through it for 5 minutes) and added to the solution of the palladium complex. The reaction vial was placed in the reaction-setup in a bath at -78°C. After the trapping of the [^{11}C]BH_3.CO as described in Example 15, the reaction was heated at 140°C for 7min, filtered and analysed for radioactivity content. The analysis of the HPLC chromatograms showed the formation of the desired [[^{11}C](4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanoyl)-benzonitrile in approximately 30% yield.

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Claims

What is claimed is:

1. A process for the preparation of radiolabelled H_3BCO comprising contacting H_3B in a suitable solvent with carbon monoxide, characterised in that the carbon monoxide is radiolabelled.

2. A process according to claim 1, wherein the process is carried out in the presence of a suitable base.

3. A process according to claims 1 or 2, wherein the production of radiolabelled H_3BCO is promoted by removal of free solvent from the mixture.

4. A process according to claim 3, wherein removal of free solvent from the mixture is promoted by condensation.

5. A process according to any one of claims 1 to 4, wherein the solvent comprises any ether or tetrahydrofuran.

6. A process according to any on of claims 1 to 5, wherein the solvent comprises diethyl ether, dioxane or tetrahydrofuran.

7. A process according to any on of claims 1 to 6, wherein the solvent is tetrahydrofuran.

8. A process according to any one of claims 1 to 7, wherein the base is triethylamine, N-Methyldibutylamine, M-Methyl-2,2,6,6-tetramethylpiperidine or *N,N*-di-isopropyl-ethylamine (DIPEA).

9. A process according to any one of claims 1 to 8, wherein the carbon monoxide is radiolabelled with ^{11}C, ^{13}C, ^{14}C ^{15}Oor ^{18}O.

10. A process according to claim 9, wherein the radiolabel is ^{11}C.

11. A process for preparing radiolabelled compounds by carbonylation using radiolabelled H_3BCO prepared according to any one of claims 1 to 10 as a donor of radiolabelled carbon monoxide.

12. A radiolabelled compound prepared using a process according to claim 11.

13. Use of a radiolabelled compound according to claim 12 in imaging techniques.

14. Use according to claim 13, wherein the imaging technique is selected from positron emission tomography, modified single photon emission tomography or autoradiography.

15. Use according to claim 14, wherein the imaging technique is selected from positron emission tomography.

16. A product of a process according to any one of claims 1 to 11.

17. A composition comprising a radiolabelled compound according to claim 12.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 February 2005 (17.02.2005)

PCT

(10) International Publication Number
WO 2005/014479 A3

(51) International Patent Classification:
A61K 51/02 (2006.01) *C07B 59/00* (2006.01)
C01B 35/10 (2006.01)

(21) International Application Number:
PCT/EP2004/008830

(22) International Filing Date: 5 August 2004 (05.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0318728.3 8 August 2003 (08.08.2003) GB
0416141.0 19 July 2004 (19.07.2004) GB

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(74) Agent: **KNIGHT, Lucie Viktoria**; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
1 June 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING RADIOLABELED COMPOUNDS

(57) Abstract: A novel process for preparing radiolabelled compounds by incorporation of radioactive carbonyl groups into precursors, which are then used to make the radiolabelled compounds. These radiolabelled compounds have a number of uses including in vivo imaging techniques such as positron emission tomography.

WO 2005/014479 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/008830

A. CLASSIFICATION OF SUBJECT MATTER
C01B35/10 A61K51/02 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C01B C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, INSPEC, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JONES L H ET AL: "Potential constants of borane carbonyl" JOURNAL OF CHEMICAL PHYSICS USA, vol. 70, no. 2, 1979, pages 749-757, XP008041698 ISSN: 0021-9606 page 749, right-hand column - page 750, left-hand column ----- -/--	1-10,16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2006	04 04 2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rigondaud, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/008830

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ALBERTO R ET AL: "SYNTHESIS AND PROPERTIES OF BORANOCARBONATE: A CONVENIENT IN SITU CO SOURCE FOR THE AQUEOUS PREPARATION OF [99MTC(OH2)3(CO)3]+" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 123, 13 March 2001 (2001-03-13), pages 3135-3136, XP001120003 ISSN: 0002-7863 cited in the application page 3135, right-hand column	1-10,16
A	VENKATACHAR, A. C. ET AL: "Microwave spectrum , structure, quadrupole coupling constants and dipole moment of carbon monoxide- borane" JOURNAL OF MOLECULAR STRUCTURE, vol. 38, 1977, pages 17-23, XP002314162 page 18; table 1	1
A	WO 02/102711 A (KIHLBERG, TOR; LAANGSTROEM, BENGT) 27 December 2002 (2002-12-27) the whole document	11-17
A	ZEISLER S K ET AL: "Conversion of No-carrier-added [<11>C]carbon Dioxide to [<11>C]carbon Monoxide on Molybdenum for the Synthesis of <11>C-labelled Aromatic Ketones" APPLIED RADIATION AND ISOTOPES, ELSEVIER, OXFORD, GB, vol. 48, no. 8, August 1997 (1997-08), pages 1091-1095, XP004094769 ISSN: 0969-8043 cited in the application the whole document	11-17
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A	WO 01/25243 A (MALLINCKRODT INC; ALBERTO, ROGER, ARIEL) 12 April 2001 (2001-04-12)	
P,X	AUDRAIN, HELENE ET AL: "Utilization of [11C]-labelled boron carbonyl complexes in palladium carbonylation reaction" CHEMICAL COMMUNICATIONS (CAMBRIDGE, UNITED KINGDOM) , (5), 558-559 CODEN: CHCOFS; ISSN: 1359-7345, 2004, XP002372602 the whole document	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/008830

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10, part of 16

The problem solved by the first invention is to provide:
- a process for the preparation of radiolabelled H3BCO by contacting H3B in a solvent with a radiolabelled carbon monoxide,
- the product so produced.

---

2. claims: 11-15, part of 16, 17

The problem solved by the second invention is to provide:
- a process for preparing radiolabelled compounds by carbonylation using a radiolabelled H3BCO as a donor of radiolabelled carbon monoxide,
- a radiolabelled compound so produced,
- its use in imagine techniques,
- a composition comprising such a radiolabelled compound.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/008830

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